other words, a shorter duration of high-frequency oscillation may be better as long as you can tolerate it, so to speak, before coming back to the accepted therapy of your colleagues. That was one question. Do you have any information on that?

DR. STEWART: One thing I know of, and again I am not a basic scientist, but I did see a paper that I know is in press currently, in the Journal of Applied Physiology, where they looked at conventional versus high-frequency oscillation and showed that although you could achieve with really aggressive conventional ventilation, similar oxygenation profile, physiologic benefit with CO_2 and oxygenation, that the markers of lung inflammation in terms of cytokines was worse with the conventional group.

So, some people argue you can do everything you can do with conventional that you can do with the oscillator, but however, there may be inflammatory markers that you are actually causing with conventional ventilation that you don't get perhaps with high-frequency oscillation.

But in terms of adult experience--and Alex may know more about this than I do--I haven't seen anyone measuring markers or doing pathology that we

don't see at the bedside.

DR. DERDAK: In the animal models, there have been studies in whole animal models using the same mean airway pressure, high frequency versus conventional, that have looked at, for example, lavage levels of tumor necrosis factor, of platelet-activating factor, of IL-8 macrophage activation markers, which have suggested that in the whole animal model, that high frequency has less of an inflammatory effect, at least with those primers I just mentioned.

We just presented an abstract at ATS this past meeting, and also presented it at the Snowbird, doing exactly what you just suggested, I am surprised you asked that question. We are growing human lung fibroblasts on membranes and subjecting them to stretch at 0.5 hertz simulating 30 breaths a minute or conventional ventilation versus 5 hertz at 300 breaths a minute, and analyzing a number of parameters on these lung fibroblasts, such as apoptosis, intracellular extra-structural damage, and looking at the supernatants for cytokines like IL-6 and TGF beta.

We had some preliminary data that we presented at the ATS on the IL-6 data showing that

the IL-6 was higher in 0.5 hertz versus the 5 hertz stretch, but was different if you look at neonatal lung fibroblasts versus adult lung fibroblasts, have seen difference in effects between where the fibroblasts came from.

The reason we chose fibroblasts is because we have just had somebody in our laboratory growing them, and they are very nice for those studies because they are adherent to the membrane. It is difficult to look at nonadherent cells and subject them to stress.

I think that is an interesting line of research, though, because you could ask the question, given that you could, for example, create a similar blood gas with two different kinds of settings on the oscillator, is there one that might have a biological benefit as opposed to just the blood gas benefit, and getting at the hertz question versus the delta P, for example. It is assuming that both might give you a similar blood gas, would one be better than the other for biologic injury.

We are trying to do that in vitro. I think ultimately, those things will have to be done in the whole lung model, because so many things

affect the processes, as you know.

DR. MUELLER: Very good. The second concern I had relates to your condensate trap that you have within your system. Obviously, that is not affecting just the air flow and distribution of humidity or, if you prefer, aerosols that might be produced in the distal lung, but also more proximate.

Do you have any data on the, let's say, reverse infection capability between your condensate trap and the patient? In theory at least, a simple mind might say, well, your patient may be generating, let's say, bacteria from an acute insult of some sort, which then gets trapped down into the collector. Then, the patient gets treated with antibiotics, which cure his infection, but your collector, unless it is changed frequently enough, might be the source of reinfection.

Do you have any information on reverse contamination or any data in terms of the frequency of changing that trap, that might be helpful to assuage your concerns about reverse contamination?

DR. DERDAK: That is a good question. I don't know of data looking at nosocomial pneumonia rates, for example, or ventilator-associated

pneumonia rates in the patients that have been treated with high frequency. Perhaps there is some in the pediatric data.

DR. PROUGH: Speak into the microphone, please.

DR. DERDAK: I am not aware of data on ventilator-associated pneumonia rates during high frequency, which I think partly this gets at, whether there is a higher potential for contamination of the airway from the design of the circuit or specifically the collection trap that is beneath the diaphragm, which periodically is emptied.

It is a gravity trap, which is beneath the plastic one of the diaphragm, which it is well below the ventilator, so in my view, it is almost impossible to have that fluid, you know, you have to literally disconnect it and hang it up to have it then contaminate the circuit as opposed to conventional ventilator circuits with traps. When you manipulate the circuit, oftentimes if you are not careful, you can spill a bottle of water into a circuit.

But I don't know the answer to that question. Do you know of any evidence on pneumonia

rates or circuit contamination, whether it would be--I don't have theoretic reasons to suspect it would be higher than on conventional ventilation because of the location of the trap and its fixture to the ventilator. I would think it would have less potential than mobile traps that are not fixed.

DR. MUELLER: Sudden increases in the bias flow, for instance, if you did have some valve pop off or the dump valve, it might change pressure and get periodic, you know, if there is some water halfway down the little tube draining into the thing, it might pop back up and get aerosolized in the process.

MR. STENZLER: In fact, the location of the water trap being below the diaphragm, the tube going to that is 1/8th ID, 1/8th inch ID, so it is a very small diameter tubing, high-resistant tube. The gas actually enters the circuit proximal to the patient. That is actually on the back side of where the gas enters. So, if a valve popped, gas would be going to the patient, not through that. It wouldn't suck any gas out of that, any fluid out of that, and the rate at which water accumulates, condensate accumulates is set at a high enough rate

that that has to be emptied every few hours, so the likelihood of any materials staying in there for any prolonged period of time is also unlikely.

DR. HUDSON: Following up with that, is there any evidence that you need to change the circuit any more frequently than a regular conventional ventilator?

MR. STENZLER: No.

DR. MUELLER: Not by your directive as far as changing it in your file material. The last thing you mentioned, that there were no changes in the instructions to users, and yet in one of the supplements that was requested by the Secretary, there was a discussion about letting down the cuff if you can't get the CO_2 down, and so forth, but I couldn't find that in at least what was included in the material we got as far as how to lower your CO_2.

It went through the changes in airway pressure and driver force and slowing the frequency, and so forth, but I didn't see letting down the cuff or a discussion of that, and yet it seems to be important in the pediatric patient.

MR. STENZLER: It believe it is Chapter 8, at least in the revised edition, I believe it is in

there.

DR. MUELLER: I missed it in mine anyway.

DR. PROUGH: Dr. Roizen.

DR. ROIZEN: I have two questions that relate to my conversations with pediatricians. One was that they said this is, if you will, an imperfect art in pediatrics and neonatal, and there is a great deal of clinician art in it, so one of the ways they judge adequacy of ventilation is that you vibrate the hips, and not the toes, and while that is clinical art, it doesn't make it into either the teaching module or any of the chapters that I saw.

I wondered, if there clinical art on the adult side, like that, that should be in the version, and I guess the corollary question is, is there any value to having pediatric or case studies in the teaching module rather than just adults as it looks like are proposed.

DR. DERDAK: That issue of the initial setting of the delta P to titrate just vibration or to the thigh is just that. It is simply an initial setting.

Another art, rule of thumb that we observed in the rescue study, and even in this

study when we go back and look at our data, is that another way to do that is to roughly set the delta P at 20 plus the patient's PCO_2 as a rule of thumb number as to which to set the delta P.

I think it is quite subjective to decide is the middle of the thigh shaking or is it just down a little bit past the mid-thigh, or how much wiggle we have. Again, that is just an initial setting for the first 10 or 15 minutes to then get a blood gas, because you are ultimately going to be adjusting the delta P subsequent to that based on your PCO_2, so it is not something that you continue to titrate so much as you would based on a PCO_2, so it is an initial setting.

Again, outside of protocols, we use a general rule of thumb as 20 cm plus the PCO_2. That is probably not in the Manual, but we will be putting that into review type articles.

DR. STEWART: If you think about it, it is very similar to what I currently do with conventional now, and when we intubate a patient, we guesstimate rate and tidal volume, and we ask for a blood gas relatively fast.

Ours is like Steve's experience, we don't use that same number, but we look at the wiggle.

The question comes in, with different body types, people will wiggle at different rates. So far our rescue experience has been terrific in terms of CO_2, and we haven't had CO_2's getting out of control in that time window, so we have had time to adjust.

The reason to sort of standardize or get a feel for how much the patient is wiggling at the bedside, I guess is where the art comes in, is when they do run into problems when they are paralyzed, if they do, like a right main stem bronchus intubation or dislodged endotracheal tube or a plugged endotracheal tube or pneumothorax, is that you are aware of how much they are wiggling before, and look for changes in that wiggle factor, we call it.

DR. ROIZEN: The second question is there was not much dealing with humidity problems in the study. Were they nonexistent or were they just equal between the two groups? So, it is inspissation, or was a minor part, but I didn't say a very extensive discussion on that, which I guess is a problem or at least in the pediatric population.

MR. STENZLER: The humidity problem for high-frequency ventilation in the past was tied to

jet ventilators, which used zero humidity gas ejected out of a needle, a very low humidity.

With the oscillator, all of the gas all goes through a standard humidifier, because it is only traveling up to 60 liters per minute, relatively slow compared to what we oscillate it at. Then, that humidified gas goes into the circuit where the driver actually accelerates the full humidified gas.

Humidification is typically not a problem if people use the humidifiers correctly, and that is always one of the issues, because some of the manufacturers suggest that the humidifiers be used with different temperature settings than you would use for high frequency. We have recommendations for temperature settings for a conventional humidifier.

DR. STEWART: We were really worried when we first got into it part time--tracheobronchitis, and we took to doing bronchoscopy on all of our early patients, and we stopped because it wasn't an issue. In fact, I find it, compared to my experience with the jet previously, a lot better in terms of humidification.

Back to your question about the art, I

think there was art with the jet, to be honest. It is simple to manage. If you have any trouble with oxygenation, you adjust your mean airway pressure, when you are having trouble with ventilation, it is your hertz and your delta P. It may be a lot less of an art, it is quite easy to use.

DR. PROUGH: Dr. Hudson.

DR. HUDSON: My questions that I wanted to understand better was the training aspect, and it is not the content of the training, but who gets trained and what is the commitment to that? Obviously, that is going to be partly up to the center that you are selling the ventilators to, and the practice varies so much from center to center as to who gets to use the ventilator, so who gets trained right now?

You had mentioned docs, and I am assuming then that it would either be the medical director of Respiratory Care or someone instrumental in Critical Care, but also I assume the respiratory therapist.

Could you tell us more about that?

MR. STENZLER: The programs that we have, as I said, we basically run two programs for training. We run a very formal two-day program

that is not at the hospital. It is typically at one of our training facilities where the physician and/or therapist come to be trained, and have an animal laboratory.

We have also done for many facilities on-site training programs including animal laboratories where a hospital has enough people, and they say we would like to do it on site, so we can get a large group of physicians and our therapists trained.

Above and beyond that, we do send out clinical people to every hospital to train the respiratory therapists in the general management principles, care and maintenance of the machine, how to manage the patients, but those don't always include animal facilities with physiologic models because of the limitations at the facilities themselves, but basically, every center does get trained by qualified people, and usually, all of the therapists that are managing patients.

DR. HUDSON: I guess the other question I have about that, maybe, Mike, you can answer this, this is my first time on this sort of panel, what is the commitment, then, for training those people if this gets approved? How does that continue on,

and does that have to be a condition, or is that understood from the application?

DR. BAZARAL: As far as I understand it, the material that they have submitted now, for example, would be a commitment that the company has made pre-approval, if approval is what happens, and that commitment would be conceivably audited, but at least certainly expected of the company, and any changes to that may depend on your recommendations, either as conditions or simply recommendations.

DR. HUDSON: So, your current commitment is to train every place that you sell machines to.

MR. STENZLER: Well, let me qualify that. Our commitment is train every place that we sell machines to that are willing to purchase the training. We don't pay for flying people into other facilities to a training center for training. Like with any other device, you can buy educational services. The on-site training is done at no cost, and that we always do, and we have done always in the past.

DR. HUDSON: The other isn't a question, it is something that we may discuss further, and it is a dilemma and as you commented, the primary endpoint wasn't forced on the company, it was

something the company and investigators and the FDA came up with together, but I find the primary endpoint inappropriate, and not very compelling to evaluate clinical safety and efficacy, but some of the other data more compelling, particularly the six-month endpoint, and which could include any respiratory support just because of the nature of the disease and what we know about the history, and also then, the harder, secondary endpoints, which are mortality and the complication rate, so I think that is something we have to discuss as a panel more.

DR. PROUGH: Do any of the panel members have any other questions or comments? Dr. Schroeder.

DR. SCHROEDER: Yes. I noticed that when you listed the studies, other studies, trials that you have currently going on was one with nitric oxide. Do you have any data or information on other tracheal-administered drugs, specifically, delivery of nebulized or aerosolized drugs with the system?

MR. STENZLER: We don't presently have specific data on that. The corporation does have development programs on new nebulizing technology,

capable of delivering drugs endotracheally, but that is under development, not just for high frequency, but we do have a program.

DR. SCHROEDER: So, for the patients that were in your trial, you never had to administer beta agonists or anything, or you didn't do it, or you did it and hoped it worked?

MR. STENZLER: I don't believe that there were beta agonists delivered to any of the patients during the trial.

DR. PROUGH: Dr. DeMets.

DR. DERDAK: Asthma and COPD are definitely listed exclusions.

DR. SCHROEDER: I noticed those were exclusions, but there are other patients than those specific diagnoses that sometimes require a beta agonist.

DR. PROUGH: Dr. DeMets.

DR. DeMETS: If we are going to focus on some of the other outcomes, as has been suggested, a technical point. You can't really just focus on--I will pick failure to wean as an example--because there is censoring going on, informative censoring, mortality.

So, if you are really going to focus on

it, the analysis we need is death plus failure to wean, or death plus--I mean, you understand? There is a censoring, and, in fact, it is all going in the same direction, in a favorable direction. I am not worried that our conclusions will be different, but we ought to go through that exercise, or somebody ought to go through that exercise.

DR. PROUGH: Dr. Kirton.

DR. KIRTON: I know there is contraindications with asthma and COPD, and it is obvious that the humidification concerns that plague the jet ventilator seems to have been resolved with the oscillator.

Are there any recommendations in regards to the amount or copiousness of tracheal secretions as part of the instructions to users?

DR. DERDAK: I might address that, and I think it is at the training and the use of the oscillator. Our recommendation, at least at our study site, was when oscillation is initiated, that if the patient is going to have bronchoscopy or suctioning done, that should be done prior to putting them on the oscillator, particular bronchoscopy to verify patency of the tube to obtain secretions, so that we don't have to then

derecruit the lung once they are on high frequency, and that when we initially place them on the oscillator, we attach the circuit direct in line without a suction device to establish that we can ventilate the patient well, and then put an in-line suction adapter.

Again, as we learned with the additional experience of treating more patients, these patients do ventilate well, but the issue of how often to suction, I think is also a question that we don't have a clear answer to. Clearly, when you suction and induce negative carinal pressure, you run the risk of desaturation, of derecruitment of lung, it is my bias or opinion that suctioning ought to be minimized in these very sick patients unless there is obvious gross secretions in the airway, because you may do more harm than good by doing that.

That is part of what I would consider part of the clinician's training package on how to use this device, and when would you do suction, how do you recognize a tension pneumothorax if it occurs on the oscillator, how to recognize a main stem intubation or a mucus plugging of the endotracheal tube, how do you know that it is occurring.

I think those are all vital parts of the training that we should offer.

MR. STENZLER: I should point out that if you remember the slide I put up of the eight prospective, randomized, controlled trials of the oscillator, only two of those trials were actually used for the approval process through the FDA, and SensorMedics continues to sponsor both randomized, controlled trials, basic science research, and technical trials or technical studies to optimize, to determine and better understand how to use our devices, so that the fact that you may grant us approval to introduce the 3100B into clinical practice, it is not the end of our research efforts on this device.

In fact, the Courtney Duran trial, which just concluded, is basically 10 years after our approval for neonatal application, and that was co-sponsored by SensorMedics with almost a quarter of a million dollars of support 10 years after the device was approved, just to get a better handle on the application and use of the device.

So, I think you can be assured that we will continue to try and have a better understanding of the device and how to use it.

DR. PROUGH: If there are no further comments, this might be a good time to take a 15-minute break, come back at quarter of 3:00. When we do come back, it will be the open public hearing, and I would like to request that the sponsors take the seats that are reserved for them behind the table.

[Recess.]

Open Public Hearing

DR. PROUGH: Are there any members of the public who would like to make a presentation or have comments related to the device under review?

[No response.]

DR. PROUGH: If not, if no one from the public would like to make any comments, then, the open public hearing is now closed and we will proceed to recommendations and voting.

Before the panel discussion for recommendations and voting begins, I would like to ask Mr. Stenzler if there are additional comments or presentations that SensorMedics would like to make.

MR. STENZLER: Not at this time. Thank you.

Recommendations and Voting

DR. PROUGH: Thank you.

Let's move on then.

Mr. Noe, could you please show the first question for the panel.

1. In light of current practice, please discuss whether the control group in the SensorMedics trial alone is appropriate and reasonable for evaluation of the Model 3100B High-Frequency Oscillatory Ventilator.

The floor is open for discussion. I think we need we move this toward yes or no.

DR. HUDSON: I think I discussed my opinion before. I think that it is actually. I think that the patient selection was appropriate, and I think that the standard of the conventional management was appropriate for the time of the study and actually up until just recently. So, I would say yes.

DR. SESSLER: I agree. In fact, I think it still represents practice, perhaps not the standard that we would all like to have quite yet, but I think it does represent broad practice currently, as well.

DR. PROUGH: Is there any disagreement with that answer to Question 1?

[No response.]

DR. PROUGH: In that case, may we have the second question.

2. Please discuss whether the information presented provides reasonable assurance that the Model 3100B is safe and effective.

I think this is essentially the recommendation that we will be asked to make about approval, so I will defer this question as part of the discussion and voting regarding recommendations about approval.

Why don't we move to the third question.

3. Please comment on the labeling provided for the Model 3100B. Specifically, please discuss:

a. whether Chapter 8 of the Operator's Manual, which instructs the user on treatment strategy, adequately reflects the protocol and data from the SensorMedics trial;

b. whether the two-day training program described will adequately prepare physicians to use the Model 3100B; and

c. whether any other specific changes should be made to the labeling of the device.

The floor is open for discussion.

DR. SCHROEDER: I guess I have just one comment.

DR. PROUGH: Go ahead.

DR. SCHROEDER: The issue about the labeling of the device, I guess I would bring up again my reservation about the delivery of tracheally-administered drugs, that there should be some mention in the labeling about that, that we do not have data, we don't know if they are adequately delivered, and should be used with caution or something along those lines.

DR. PROUGH: Why don't we take the three parts of this question really in order. We have one comment about labeling. Are there any other issues about labeling?

DR. SCHROEDER: I am sorry. I have just one other comment. Patients with asthma and COPD were excluded from this. I guess I would put that out. I didn't see any comment about those, reservation of use of this device in those patients in the labeling. I may have missed it. But should there be something listed that we do not know whether or not this is safe and effective in that subset of patients?

DR. PROUGH: Does anyone recall if that

specifically was or was not mentioned?

DR. ROIZEN: I did not see it mentioned.

DR. SCHROEDER: Whether patients with asthma or COPD were excluded from the study, and I did not see anything in the labeling saying that we don't know if this is safe and effective in that subset of patients.

DR. PROUGH: I think that all that is emphasized is acute respiratory failure and acute respiratory distress syndrome.

DR. ROIZEN: I guess the corollary which goes along with your question on that earlier is on drug, that it isn't known whether drugs that are aerosolized are available for delivery yet. I guess that should be under that first dash of that question.

DR. PROUGH: Could you repeat that, Mike? I am sorry. I heard you. I am not sure I quite understood.

DR. ROIZEN: We don't know whether the company answered to Becky's question. At least I took it to mean that they did not know whether aerosolized drugs would be able to be used with this system yet, so that should be placed under Chapter 8 of the Operator's Manual, if you will, in

that part of the question, because it just isn't known yet.

DR. PROUGH: In general, are there any other comments about whether Chapter 8 of the Operator's Manual adequately reflects the protocol and data from the SensorMedics' trial? Are we comfortable with Chapter 8 as revised?

[No response.]

DR. PROUGH: If there aren't any comments, let's move on to the two-day training program. Do we consider that adequate? Any concerns about its adequacy?

DR. ROIZEN: They seem to have used it for the pediatric, and it seems, at least in my conversations with people who practice neonatal and pediatric ICU, it seems to be an effective training session.

DR. PROUGH: Any other comments about that? Any other comments about labeling?

[No response.]

DR. PROUGH: Let's move on to the fourth question.

4. Please discuss whether additional clinical follow-up of postmarket studies are necessary for the Model 3100B.

DR. KIRTON: I would say yes, but it appears from the response from the company that they will continue to support ongoing studies, which will address a lot of the art and user issues evolving around this technology.

DR. DeMETS: How about a quick comment?

DR. PROUGH: Yes.

DR. DeMETS: I guess my comment is related somewhat to my point of view on Question 2, but I think that we have established, let's just say, probably safe and probably not inferior, but I don't think we know anything about clinically effective or clinically beneficial.

I mean the criteria, even the most generous interpretation, we have missed on every one of them, so I don't think we can say we have device that we know is clinically superior. So, there is room for some further studies to further evaluate that question.

DR. ROIZEN: What I understood was the least burdensome rule or interpretation, that there may be likes that we have, or desires, but those are not from what I gather to be part of the postmarketing studies unless they are really required for approval, is that correct?

DR. ZUCKERMAN: Yes. This is Bram Zuckerman from FDA. In terms of where we are right now in our postmarket studies surveillance program, we need to view it and direct it within the context of the least burdensome provisions, so that if there is a recommendation from the panel for some type of postmarket study, the question would need to be focused and really well thought out, et cetera.

I think in answering Dr. DeMets' concerns, when the discussion does go to what is necessary for voting on safe and effective, the reasonable assurance of safety and effectiveness does not necessarily include superiority, and you will need to again review our regulatory definitions and think about things in the device law context.

DR. PROUGH: Any other comments about the fourth question?

DR. GARMAN: Yes. I don't think there is anything here to warrant requiring additional research. I think additional research will be in the "nice to know" category. That is my position.

DR. PROUGH: Any other comments?

[No response.]

DR. PROUGH: Mr. Noe, except for the

deferred question about safety and effectiveness, does the panel need to provide additional discussion of the FDA questions?

MR. NOE: I think that is sufficient, thank you.

DR. PROUGH: Thank you.

Mr. Stenzler, do we need to look at anything else?

MR. STENZLER: I don't believe so. I believe that we have presented everything that the panel would need to evaluate. Thank you for your attention.

DR. PROUGH: Thank you.

We will now proceed to the formal recommendation about approval.

Dr. Bazaral, will you please read the definitions and voting instructions to the panel.

DR. BAZARAL: I will read the Panel Recommendation Options for Premarket Approval Applications.

The Medical Device Amendments to the Federal Food, Drug, and Cosmetic Act, as amended by the Safe Medical Devices Act of 1990, allows the Food and Drug Administration to obtain a recommendation from an expert advisory panel on

designated medical device premarket approval applications, PMAs, that are filed with the Agency.

The PMA must stand on its own merits, and your recommendation must be supported by safety and effectiveness data in the application or by applicable publicly available information.

Safety is defined in the Act as reasonable assurance based on valid scientific evidence that the probable benefits to health under the conditions of intended use outweigh any probable risks.

Effectiveness is defined as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses, and conditions of use when labeled, will provide clinically significant results.

Your recommendation options for the vote are as follows:

1. Approval if there are no conditions attached.

2. Approvable with conditions. A panel may recommend that the PMA be found approvable subject to specified conditions, such as physician or patient education, labeling changes, or further analysis of existing data. Prior to voting, all of

the conditions should be discussed by the panel.

3. Not approvable. The panel may recommend that the PMA is not approvable if the data do not provide a reasonable assurance that the device is safe, or if a reasonable assurance has not been given that the device is effective under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

Following the voting, the Chair will ask each panel member to present a brief statement outlining the reasons for their vote.

DR. PROUGH: You have received the instructions. Do we have a motion? Are you about to make a motion?

DR. ROIZEN: Yes, I am. Not knowing this process as well as perhaps one would like, but I think I would make a motion that it be approvable with conditions.

DR. PROUGH: We have a motion that it be approvable with conditions.

Is there a second?

DR. SCHROEDER: I will second.

DR. PROUGH: In that case we now need to discuss conditions.

What conditions would the panel like to

add to the motion?

DR. ROIZEN: We only add one condition at a time, is that correct?

DR. PROUGH: One condition at a time, which needs to be separately voted on, and then ultimately, we get around to the final, the original motion.

DR. ROIZEN: The first condition I would like to discuss is changes in the labeling or additions to the labeling that include the asthma and COPD and drug administration processes.

PARTICIPANT: Second.

DR. PROUGH: The condition has been moved and seconded.

Dr. Zuckerman, is the condition appropriate from your perspective?

DR. ZUCKERMAN: Yes, it is the prerogative of the panel to make recommendations, and certainly we will work on these recommendations in-house.

DR. PROUGH: It has been moved and seconded. Is there any further discussion?

[No response.]

DR. PROUGH: Do we need to vote on every condition?

DR. ZUCKERMAN: Yes, at this time, and at

least enumerate the votes.

DR. PROUGH: So, the first condition why don't we begin with Dr. Hudson, and if you have specific comments about your vote, please state them.

DR. HUDSON: Yes.

DR. PROUGH: Dr. Roizen.

DR. ROIZEN: Yes.

DR. PROUGH: Dr. Mueller.

DR. MUELLER: Yes.

DR. PROUGH: Dr. Sessler.

DR. SESSLER: Yes.

DR. PROUGH: Dr. Kirton.

DR. KIRTON: Yes.

DR. PROUGH: Dr. Schroeder.

DR. SCHROEDER: Yes.

DR. PROUGH: Dr. DeMets.

DR. DeMETS: Yes.

DR. PROUGH: The vote then is unanimous that that condition be added.

DR. HUDSON: Let me make sure I understand. It was to mention that we don't know about it.

DR. ROIZEN: Correct.

DR. PROUGH: I guess it is really 7 yes.

Is there another condition?

DR. ROIZEN: The second condition was that the data be analyzed with supplemental O_2 via cannula extracted from the primary endpoint. I think that is the basic condition. In other word, as I understand, Mike, and maybe you can correct me, that you can put conditions relating to analysis of existing data.

DR. BAZARAL: I presume that would just go on the labeling because I don't know what else we would do with it.

DR. PROUGH: There is a motion.

Is there a second?

DR. SCHROEDER: I am sorry, I don't mean to be obtuse, but I am not quite sure I understand.

DR. ROIZEN: The data we don't have, at least as I looked at it, to approve efficacy, to make sure that we hit Dr. DeMets' and perhaps all of our concerns in this non-inferiority understanding is that the endpoint not cross a zero when you analyze it that way, but most of us were, at least I thought, uncomfortable with O_2 by cannula being in that hard endpoint area of requiring mechanical ventilation, death, or CPAP.

DR. SCHROEDER: I just think we need to be

a little more specific about how we state it.

DR. ROIZEN: I wanted to be, but I didn't know how we do this.

DR. HUDSON: I don't know. It hasn't been seconded, so I don't know if it is appropriate. It seems to me that we already have the data. We heard the number of patients on mechanical ventilation, and I think we just have to decide on that when we decide on the question of safety and efficacy.

DR. ROIZEN: I didn't hear that data. Did they give it to us?

DR. HUDSON: What they had was when you take the mortality rates and then the overall support data, there were 41 patients on high-frequency oscillation that had some sort of respiratory support, and 62 percent I think of those were on mechanical ventilation, and there were 21 patients on conventional ventilation, and 73 percent of those, the support was mechanical ventilation, so subtracting those out, you would know the number that was on oxygen.

What we didn't hear--

DR. ROIZEN: What we didn't have is the statistical analysis of that.

DR. HUDSON: We don't have a statistical analysis, but you have a general breakdown.

I guess I would think we have to just take that into account in deciding where we put those data in terms of answering the question of efficacy and safety.

DR. PROUGH: We actually I don't believe had a second on the motion unless I missed it. Was there a second on the motion? Is there a second on the motion?

[No response.]

DR. PROUGH: I think the motion dies for want of a second.

Are there any other conditions?

DR. DeMETS: I don't know how to express this in this motion, but I think we need to distinguish between establishing superiority from non-inferiority. The question isn't posed that way, but that was the hypothesis that was studied, and I don't know how to frame it in the conditions, but by the end of the day, I think that needs to be specific what we have shown and what we haven't shown.

Maybe that is just an internal in-house discussion.

DR. BAZARAL: That might be a discussion of the main motion, approvable or not approvable with or without those conditions.

DR. PROUGH: Would you like to withdraw that as a condition then or would you like to discuss it more at this point?

DR. DeMETS: If we can discuss it with the whole motion, that is fine, so take two out I guess.

DR. PROUGH: Are there any other conditions?

[No response.]

DR. PROUGH: Well, that being the case, we have a motion and a second on the original motion. We now have one condition. Is there any discussion of the motion with the condition listed as No. 1 up on the screen?

[No response.]

DR. PROUGH: If not, do you want to elaborate on your point a little bit?

DR. DeMETS: Sure. My point was that the issue of safety and effective, effective in this case sort of has two pieces to it, I believe, is it as effective as conventional therapy by the definition set forth in the protocol, and formally,

the answer to that is no, they didn't make it, but we all have discussed that we don't personally believe that the primary endpoint was as relevant as we think, and, in fact, it met that on four out of five of the other outcomes, but nowhere did it achieve superiority.

So, when you say effective, that's a fuzzy word unless you distinguish between non-inferiority and superiority.

DR. BAZARAL: I can read the definition again if that would help.

DR. PROUGH: Please do.

Effectiveness is defined in the Act as reasonable assurance that in a significant portion of the population, the use of the device for its intended uses, and conditions of use when labeled, will provide clinically significant results.

DR. SCHROEDER: That just means it says it will do what it says it is going to do. It doesn't mean it is better than anything else. It just means it says it will do it, it doesn't mean it is better than things currently in existence.

DR. BAZARAL: It can't just do what it says it is going to do, it has to provide clinically significant results when it does what it

is intended to do.

DR. SCHROEDER: So, the manufacturer is saying that it will successfully ventilate this particular population of patients.

DR. BAZARAL: And we seek your advice as to whether that is a clinically significant result and whether it is a reasonable conclusion to reach.

DR. PROUGH: Dr. Zuckerman, did you have a comment?

DR. ZUCKERMAN: Yes. I just want to state two things. As noted in the definition, there is no requirement for superiority, however, the notion of clinically significant is a very important one.

DR. SESSLER: I did some simple math if it helps, and it may not, but as far as bad outcomes, if you combine death and mechanical ventilation and exclude the nasal cannula, 61 percent on high frequency and 66 percent on conventional, addressing the question not statistically, but addressing the question in general terms that you raised in terms of excluding the very soft outcome of nasal cannula 30 days.

So, it doesn't conclude certainly that it doesn't cross the 0.1 barrier in terms of the confidence intervals, but pretty likely that it

would not, I suppose.

DR. HUDSON: It seems to me that superiority is a higher standard that you would be asking for a stronger indication on the labeling and that clinically significant here means it should be at least as good as conventional in survival to me, and not have any concerns about additional complications, so at least as safe in terms of side effects or complications.

DR. DeMETS: The only point I am trying to make is I personally would vote that we would-- well, if I follow the protocol and the formality, we didn't make the primary outcome, but I would be perfectly willing to shift to the others and say we have met the goal of not inferior, but I don't think we have shown superiority, and I will stick to that.

DR. HUDSON: I would agree with that.

DR. PROUGH: Dr. Mueller.

DR. MUELLER: Maybe I over-interpreted what Dr. Bazaral read, but I thought it meant that it was effective, in other words, it didn't say effective compared to a control group or compared to another therapy, but effective compared to no therapy, and in that case, I think it would

qualify.

DR. PROUGH: Is there any further discussion of the motion with the attached condition?

DR. SCHROEDER: I guess I would only have one other comment to make, which is I think a significant amount of whether or not it is effective or superior or whatever is going to come down to large amounts of clinical use, large groups of patients in multiple different settings to be able to see is this highly superior in this particular subset of patients in this particular setting.

I don't think there is any way we can make that generalization from this relatively small study. I guess my own personal opinion is that we have shown that it is safe, it is no worse than what people are currently doing, and I think it deserves a chance to show that it might be better in certain instances.

DR. PROUGH: Dr. Mueller.

DR. MUELLER: I think that gets back at something I was going to bring up before when you were asking for conditions, and I hated to mention, because I think reviewing the different studies

that were included for our review, both the reprints and what we have from our own clinical experience in other studies, one of the things that the field I think really lacks is some sort of longitudinal appreciation of how therapy is changing.

For instance, when we put a heart valve in a patient now, we are forced to fill out a little form and register them, and so forth, so that, in fact, if you have a retract that valve, you can come and notify the patient.

Wouldn't that be a wonderful thing to do with people who get this wonderful new ventilator.

DR. ROIZEN: They actually have it planned. They have got it in here, it has got a registry.

DR. MUELLER: I am sorry, I missed it, but I think it would be nice, for instance, if, when the patient is enrolled, that they use the same criteria that they used to enroll them in the study, and then, for a better choice, at one and six months or at five years, whenever, go back to those patients, try to go back to the patients and see what their outcome is.

DR. ROIZEN: It is a voluntary registry,

isn't it, in Toronto.

DR. MUELLER: If that is already in there, I apologize for wasting your time.

DR. PROUGH: Just to be sure that I understand, you are not proposing that as a condition?

DR. MUELLER: Well, I think it is what the field needs, I don't know. You come back to your minimum, you know, least burdensome event, is it fair to burden this company with it when no other company is burdened with it, but we know that there is a paucity of data, and as one of my mentors once said, you can do all the research you want, if you do clinical research, don't ever study anybody in the ICU.

I think that the only way you are ever going to get any data, crude and ugly as it may be, is if you simply have a list when a new device comes out or a new intervention, and try to get some handle on what the numbers are.

You are not comparing it to anything except itself, but if you find out that, in fact, the utilization tallies off and disappears after five years, well, then it is probably not very helpful for whatever reasons, and then you can go

after what those might be, but if you keep absolutely no track as to how the population is doing or what is appropriate in the specialty, then, I think you are only saddling yourself with delaying getting that knowledge and those hints at how to intervene with the next study, delaying those studies until you need them at a later date.

DR. PROUGH: Is the panel ready to vote?

In that case, why don't we proceed to vote on the motion of approval with the stipulated condition. Why don't we start with Dr. Hudson.

DR. HUDSON: I vote for approval. Do you want to have us give the statements now?

DR. PROUGH: If you have the statement you would like to make, that is fine.

DR. BAZARAL: Let me add that just because of the formality, and I apologize for that, we should be clear that if you are voting for approvable with this condition, then, that would be what you would have to say explicitly.

DR. HUDSON: I vote for approval with the condition and the labeling change.

DR. PROUGH: Dr. Roizen.

DR. ROIZEN: I vote for approval with the condition.

DR. PROUGH: Dr. Mueller.

DR. MUELLER: Approval with that condition.

DR. PROUGH: Dr. Sessler.

DR. SESSLER: I vote for approvable with condition.

DR. PROUGH: Dr. DeMets.

DR. DeMETS: Vote in favor.

DR. PROUGH: Dr. Kirton.

DR. KIRTON: I vote for approval with the labeling condition.

DR. PROUGH: Dr. Schroeder.

DR. SCHROEDER: I vote for approval with the one condition.

DR. PROUGH: The results as I heard it are 7 in favor and none opposed.

DR. PROUGH: Would folks want to provide their rationale?

DR. HUDSON: My rationale is that I think it was shown to be safe in this study and that there were no more complications than conventional ventilation, and in terms of efficacy, particularly in the way that Dr. DeMets has phrased this or couched it, certainly non-inferiority, that the outcome was at least as good as conventional in

terms of mortality with a trend towards survival benefit.

The third is that I think it also carries a conceptual or theoretic basis for possible additional benefit in the way you could apply the practical, the open lung theory of mechanical ventilation for acute lung injury patients. That remains a theory, and that this is a benefit in applying it is still hypothetical, but at least it has a conceptual reason why it might have an additional benefit, and I think that is important, as well.

DR. PROUGH: Dr. Roizen.

DR. ROIZEN: I felt the demonstration of safety was clear. I felt the demonstration of efficacy was not clear, but tended towards enough approvability that I voted for it, and the unclearness was that the primary endpoint chosen in 1996, or whenever it was chosen, I thought was an unfortunate choice, but the secondary endpoints did show non-inferiority, and based on that and the likelihood that the other analysis that the panel I think really wanted, the one without the cannula, would also indicate non-inferiority, led me to vote in favor of this.

DR. PROUGH: Dr. Mueller.

DR. MUELLER: Yes, I voted for it because I feel that it is no worse than the options currently available with ventilatory devices, and I believe it will be a significant advantage.

DR. PROUGH: Dr. Sessler.

DR. SESSLER: I think it is going to be quite useful for our patients. First of all, I think the rationale is very solid. The safety record in the clinical trial was very solid. When I took what I consider to be useful endpoints for efficacy, granted, unfortunately, that was not the primary endpoint, but I think clearly, there was not only equivalence, but a substantial trend towards superiority. So, to me it was quite convincing.

DR. PROUGH: Dr. DeMets.

DR. DeMETS: I think I have already stated in some ways my views, but I think that the trial was well conducted, met all those criteria you want to have for a trial in this situation in terms of quality.

Two, as I said, the primary endpoint perhaps wasn't the best choice, however, I would make one point, is if you are going to choose

endpoints like that, I think you can do some things to try to minimize the bias. I am not sure that was done here, but you can have third parties review the data or something like that.

But fortunately, the other endpoints do meet the criteria although it is a little bit post hoc. I think those criteria met, so I voted in favor of it because I thought it had shown within reason to be not inferior, consistent with other data, and suggestive of a benefit.

DR. PROUGH: Dr. Kirton.

DR. KIRTON: I voted yes. I thought the clinical trial was well conducted. I thought they proved that it was safe, and I also believe these are tests of non-inferiority compared to other modalities available, and I believe also this will be quite useful for patients with severe lung injury.

DR. PROUGH: Dr. Schroeder.

DR. SCHROEDER: I voted for approval. I feel that we have seen that it is safe. I think I echo everyone else's concerns that the true effectiveness of it needs to be defined. I would really encourage the company to go ahead and with some of the more complex situations found in adults

with multiple different etiologies for their lung disease, to look at patients in a variety of settings with a variety of problems, since that is information that clinicians are going to really need to know in order to use this device safely.

DR. PROUGH: I believe that that concludes the business of the panel. I would like to thank the panelists for their participation and all the folks who made presentations for their presentations.

The meeting is adjourned.

[Whereupon, at 3:30 p.m., the meetig adjourned.]

CERTIFICATE

I, **ALICE TOIGO**, the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

Alice Toigo

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